REMARKS

The invention provides, in general, a method of promoting bone marrow cell proliferation in a mammal, the method including administering to the mammal an effective amount of recombinant human alpha-fetoprotein, wherein the recombinant human alpha-fetoprotein is produced in a prokaryotic cell and is unglycosylated.

Election/Restriction

Applicant affirms the provisional election made without traverse to prosecute the invention of Group I, claims 19 and 21. Accordingly, claims 1-18 and 22-24 have been canceled as being drawn to a non-elected invention.

Office Action

Claims 19 and 21 are pending in the application. Claims 19 and 21 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 19 and 21 also stand rejected under 35 U.S.C. § 103(a). Each of these rejections is addressed as follows.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 19 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification lacks an enabling disclosure for the claimed subject matter. More specifically, the Examiner asserts that the range of the dosage guidance is too large,

and does not enable the skilled artisan to practice the invention with a reasonable expectation of success because of the suppressive effects of HuAFP on cells of the immune system. This rejection should be withdrawn for the following reasons.

The Examiner's argument appears to be based on the belief that HuAFP suppresses the immune system, and this suppression will cause harmful side effects when administered at the upper range of the dosage indicated in the specification. However, appropriate dosages are readily determined, and indeed, required to be determined, via Food and Drug Administration (FDA)-approved clinical trials. These clinical trials assess dosages in view of the route, duration, and quantity of administration, for any human biologic drug, of which recombinant HuAFP is one. Since dosage amounts may vary considerably from patient to patient due to the particular circumstances of their disease, clinical trials are critical for determining the efficacy, and minimizing side effects, of any new drug. Indeed, such clinical trials are conducted using conventional methods, and do not constitute undue experimentation.

With regard to the Examiner's concern with respect to the suppressive effects of HuAFP, Applicant emphasizes that HuAFP has no suppressive effects on bone marrow cells, which would be expected to be hypersensitive to immunosuppressive compounds. Furthermore, Applicant points out that HuAFP suppresses the responses of only a small subset of fully-differentiated mature T-cells. This subset comprises autoreactive and cytotoxic T-lymphocytes, and not the whole population of T-cells. Administration of

HuAFP, therefore, does not affect the function of the majority of cells in the immune system. Moreover, since the upregulation of autoreactive and cytotoxic T-lymphocytes may have detrimental effects on the human body, causing a variety of different autoimmune diseases, suppression of these cells cannot be construed as a harmful effect. Accordingly, the Examiner's concern regarding the suppressive effects of recombinant HuAFP is misplaced and this basis of the rejection should be withdrawn.

As a final consideration regarding the effects of HuAFP at high dosages, Applicant points out that AFP is a natural substance which is found in large amounts in the human fetus, up to 3000 μg/ml, and up to 500 ng/ml in the bloodstream of pregnant women. [Gitlin, D. 1975. Normal biology of α-fetoprotein. *In* Carcinofetal Proteins: Biology and Chemistry, Hirai, H. and E. Alpert (eds.) pp 7-16, Ann. N. Y. Acad. Sci.; provided as Appendix A.] Therefore, HuAFP can indeed be present in significant quantities without causing adverse reactions.

Secondly, claims 19 and 21 stand rejected on the basis that the specification does not provide a working example of administration to a mammal. More specifically, the Examiner disagrees with Applicant that the instant situation is distinguishable from *In re Colianni* (Paper No. 11, page 7).

Applicant reiterates that the Examiner's reliance on *In re Colianni* is misplaced. In direct contrast to the facts found in *Colianni*, Applicant's specification on pages 19-22 provides specific examples for methods of promoting bone marrow cell proliferation.

Colianni did not include even one "single specific example of embodiment by way of illustration of how the claimed method is practiced." 195 U.S.P.Q. 152. In addition, unlike *Colianni*, Applicant's specification also provides guidance on dosages useful for promoting bone marrow cell proliferation, thus supplying information over and above a working example.

Claims 19 and 21 also stand rejected on the basis that when administered to a mammal, recombinant HuAFP will encounter not only immature bone marrow cells, but also the fully-differentiated mature T-cells in the bloodstream. This rejection refers to an abstract co-authored by the Applicant (Paper No. 7, pages 6-7), and stands on the contention that the fully-differentiated mature T-cells will be sensitive to the suppressive effects of HuAFP, such that the skilled artisan will be unable to predict modes, quantities, and length of HuAFP treatment without incurring deleterious effects.

Applicant notes that the Examiner has misinterpreted the abstract co-authored by the Applicant, regarding the suppressive effects of HuAFP on cells of the immune system. As stated above, HuAFP suppresses the responses of only a subset of fully-differentiated mature T-cells, comprising autoreactive and cytotoxic T-lymphocytes, and not the whole population of mature T-cells. Suppression of these autoreactive and cytotoxic T-cells does not cause deleterious effects; thus the issue of predicting the mode, length, and amount of HuAFP to administer so as to avoid these deleterious effects does not arise.

Finally, Applicants point out that "the first paragraph of §112 requires nothing more than objective enablement." *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). As stated in *In re Marzocchi*:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

This speculative basis for rejecting the claims is a far cry from the evidentiary- or scientifically-based reasoning on which objective truth or accuracy of the specification may be questioned. On this basis, as well, the facts in the present case compel withdrawal of the § 112 enablement rejection, and Applicant requests reconsideration on this issue.

In view of the above remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections under § 112, first paragraph, and find that Applicant's specification enables the invention as presently claimed.

Rejection under 35 U.S.C. § 103(a)

Claims 19 and 21 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hoskin et al. (1985). The Office Action (at page 4) states:

> The prior art is equivocal: '...the role of sialic acid in the immunological activity of AFP remains contentious. It is equally possible that the immunoregulatory function of AFP is determined by primary structure rather than by posttranslational modification.' (Hoskin et al., 1985, page 164). Based upon these factors, it would appear that glycosylation of AFP is immaterial to its function, and thus AFP taught in the prior art is functionally equivalent to that of the instant specification,...

The Examiner's argument is apparently based on an incomplete reading of the article. The cited Hoskin reference does not even discuss a recombinant HuAFP, much less indicate that the normally heavily glycosylated HuAFP might be biologically active in an unglycosylated state. Applicant points out that the passage quoted from Hoskin et al. has been taken out of context. More specifically, the sentence previous to the one quoted by the Examiner states "...deglycosylated murine AFP molecules are reported to lack lymphosuppressive activity."-- implying that glycosylation may well be important for AFP function. Thus it is clear that prior to the instant invention, the function of glycosylation in AFP was uncertain. Applicant's experiments as shown in pages 16-19 of the specification were therefore required to demonstrate that an unglycosylated AFP molecule retains full function. Because Hoskin cannot teach what they did not know, this reference cannot render the claimed invention obvious.

Based on the above remarks, Applicant requests reconsideration and withdrawal of the § 103(a) rejection.

Conclusion

Applicant submits that all of the claims are now in condition for allowance, which action is respectfully requested.

Applicant notes that the Examiner's Action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

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If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Sept. 30, 1998

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